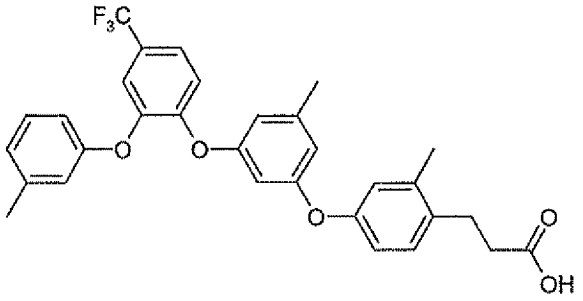
$CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{31}H_{27}O_5F_3$ 537.1888, found 537.1893.

Example 50

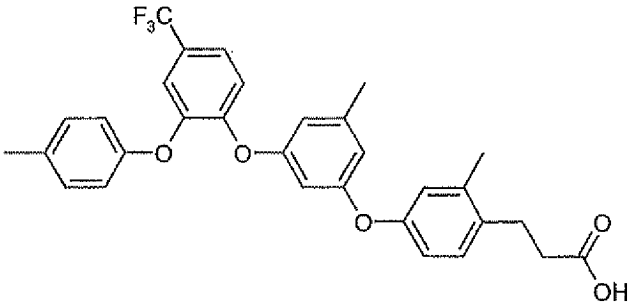
3-{2-Methyl-4-[3-methyl-5-(2-m-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with *m*-cresol as in Example 45 to afford 0.030 g (21%). ^1H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{31}H_{27}O_5F_3$ 537.1888, found 537.1879.

Example 51

3-{2-Methyl-4-[3-methyl-5-(2-p-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

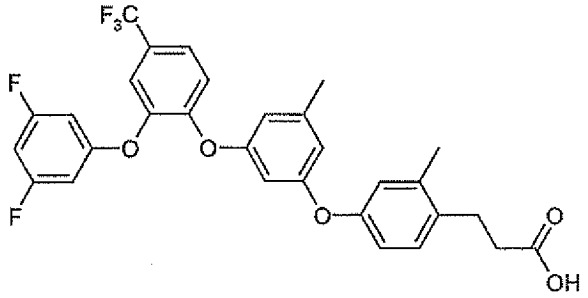


The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with *p*-cresol as in Example 45 to afford 0.035 g (25%). ^1H NMR (400 MHz,

$CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{31}H_{27}O_5F_3$ 537.1888, found 537.1874.

Example 52

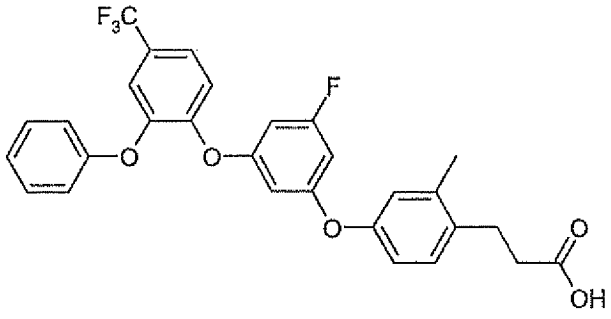
3-(4-{3-[2-(3,5-Difluoro-phenoxy)-4-trifluoromethyl-phenoxy]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with *p*-cresol as in Example 45 to afford 0.006 g (4%). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{23}O_5F_5$ 558, found 559 (M + 1, 100%).

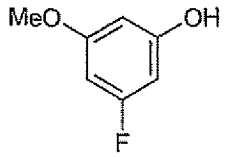
Example 53

3-{4-[3-Fluoro-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

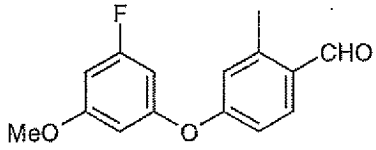
3-Fluoro-5-methoxy-phenol



A -78 ^{0}C solution of 1-fluoro-3,5-dimethoxybenzene (4.98 g, 31.9 mmol) in dry CH_2Cl_2 (50 mL) is treated with a 1 M CH_2Cl_2 solution of boron tribromide (128 mL, 128 mmol), and the mixture is warmed to 0 ^{0}C and stirred under N_2. Upon completion, the mixture is poured into ice water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using a gradient of 5/1 to 1/1 to hexanes/ethyl acetate to afford 2.40 g (53%) of the title compound. R_f = 0.49 (1/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$). MS (ES^-) *m/z* mass calculated for $C_7H_7O_2F$ 142, found 141 (M - 1, 100%).

Step B

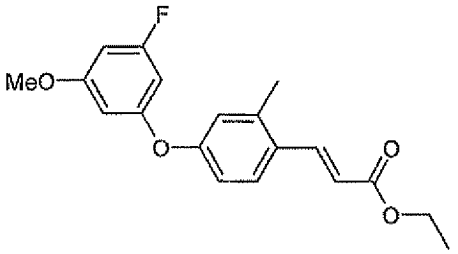
4-(3-Fluoro-5-methoxy-phenoxy)-2-methyl-benzaldehyde



A 0 ^{0}C solution of 3-fluoro-5-methoxy-phenol (2.40 g, 16.9 mmol) in dry DMF (20 mL) is treated with a 60% suspension of NaH (0.74 g, 18.5 mmol) and then stirred for 15 minutes under N_2. A solution of 4-fluoro-2-methyl-benzaldehyde (2.33 g, 16.9 mmol) in DMF (10 mL) is added dropwise, and the mixture is warmed to 60 ^{0}C for 4 hours. The mixture is cooled and acidified with 1 N HCl. The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 6/1 hexanes/ethyl acetate to afford 1.40 g (32%) of the title compound. R_f = 0.41 (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{15}H_{13}O_3F$ 260, found 261 (M + 1, 100%).

Step C

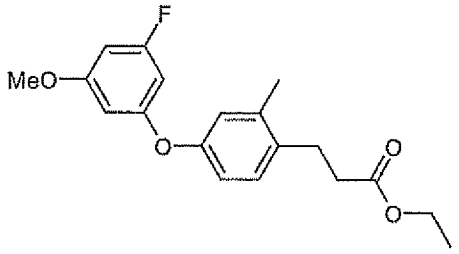
3-[4-(3-Fluoro-5-methoxy-phenoxy)-2-methyl-phenyl]-acrylic acid ethyl ester



A mixture of 4-(3-fluoro-5-methoxy-phenoxy)-2-methyl-benzaldehyde (1.40 g, 5.38 mmol), triethyl phosphonoacetate (1.45 g, 6.47 mmol), and 325 mesh potassium carbonate (2.23 g, 16.1 mmol) in ethanol (20 mL) is heated to reflux for 5 hours under N_2. The reaction is cooled, filtered and the filtrate is acidified with 1 N HCl. The mixture is diluted with EtOAc and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 0.98 g (55%) of the title compound. $R_f = 0.41$ (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{19}H_{19}O_4F$ 330, found 331 (M + 1, 100%).

Step D

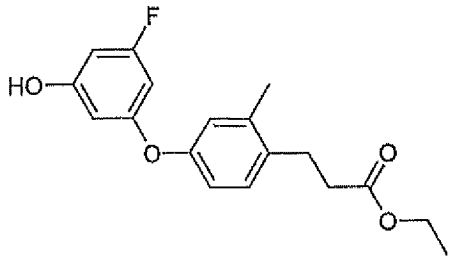
3-[4-(3-Fluoro-5-methoxy-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester



A mixture of 3-[4-(3-fluoro-5-methoxy-phenoxy)-2-methyl-phenyl]-acrylic acid ethyl ester (0.98 g, 2.96 mmol) and 10% Pd/C (0.50 g) in ethyl acetate (50 mL) is purged with N_2, and then with H_2. The mixture is stirred under a hydrogen balloon for three hours. The reaction is filtered through hyflo, and the solvent is removed *in vacuo* to afford 0.715 g (73%) of the title compound. $R_f = 0.53$ (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{19}H_{21}O_4F$ 332, found 333 (M + 1, 100%).

Step E

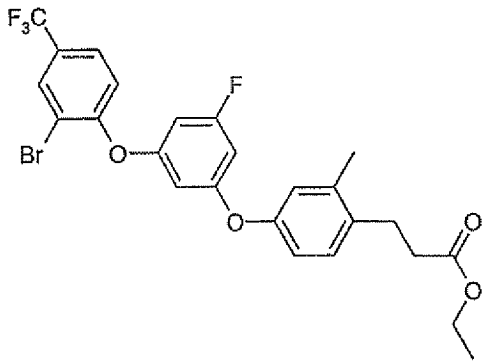
3-[4-(3-Fluoro-5-hydroxy-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester



A -78 ^{0}C solution of 3-[4-(3-fluoro-5-methoxy-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester (0.715 g, 2.15 mmol) in dry CH_2Cl_2 (10 mL) is treated with a 1 M CH_2Cl_2 solution of boron tribromide (6.5 mL, 6.5 mmol). The mixture is warmed to 0 ^{0}C and stirred for 1 hour under N_2. Upon completion, the mixture is poured into ice water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using a gradient of 5/1 to 1/1 to hexanes/ethyl acetate to afford 0.558 g (81%) of the title compound. $R_f = 0.36$ (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$). MS (ES^-) *m/z* mass calculated for $C_{18}H_{19}O_4F$ 318, found 317 (M - 1, 100%).

Step F

3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester



A mixture of 3-[4-(3-fluoro-5-hydroxy-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester (0.557 g, 1.75 mmol), 3-bromo-4-fluorobenzotrifluoride (0.425 g, 1.75 mmol) and 325 mesh potassium carbonate (0.29 g, 2.10 mmol) in dry DMSO (10 mL) is heated to 100 ^{0}C and stirred 2.5 hours under N_2. The reaction is cooled and

acidified with 1 N HCl. The mixture is then diluted with Et_2O and extracted with water. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 5/1 hexanes/ethyl acetate to afford 0.735 g (78%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{25}H_{21}O_4F_4Br$ 540, found 558 and 560 (M + NH_4, 100%).

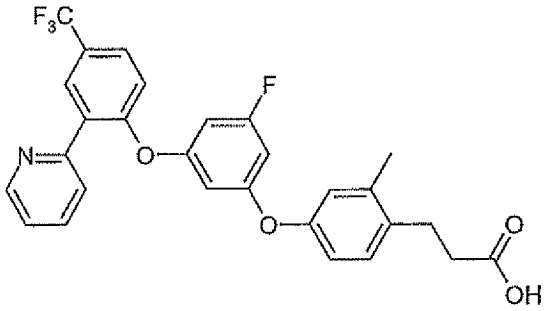
Step G

3-{4-[3-Fluoro-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

The title compound is prepare by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with phenol as in Example 45 to afford 0.080 g (28%). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{22}O_5F_4$ 526, found 527 (M + 1, 100%).

Example 54

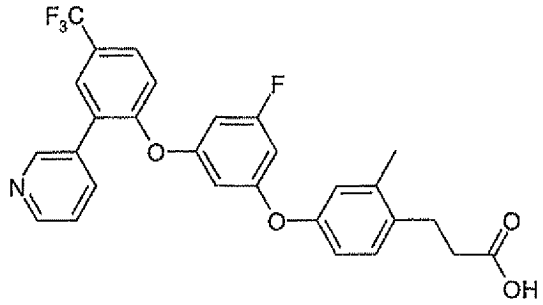
3-{4-[3-Fluoro-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepare by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 2-tributylstannyl pyridine as in Example 39 to afford 0.085 g (36%). ^1H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{28}H_{21}NO_4F_4$ 512.1485, found 512.1487.

Example 55

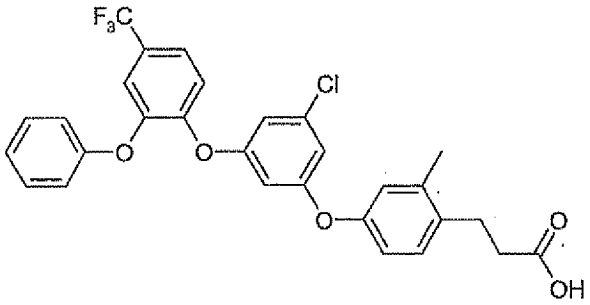
3-{4-[3-Fluoro-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepare by reacting the compound of 3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with pyridine-3-boronic acid as in Example 38 to afford 0.115 g (66%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{21}NO_4F_4$ 511, found 512 (M + 1, 100%).

Example 56

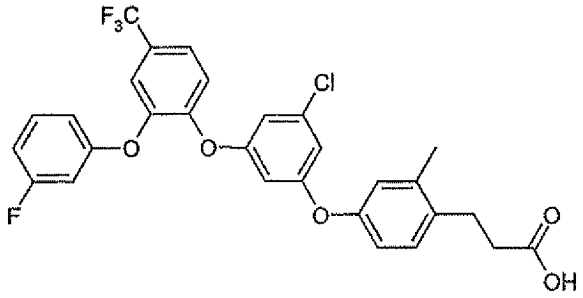
3-{4-[3-Chloro-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The compound of 3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-5-chloro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester is prepared as described in Example 56 which is then reacted with phenol as in Example 45 to afford 0.033 g (11%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{22}O_5F_3Cl$ 542, found 560 and 562 (M + NH_4, 100%).

Example 57

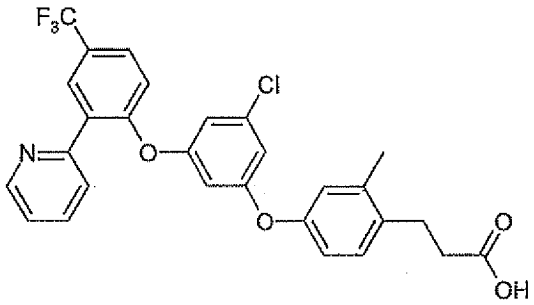
3-(4-{3-Chloro-5-[2-(3-fluoro-phenoxy)-4-trifluoromethyl-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepare by reacting the compound of 3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-5-chloro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 3-fluorophenol as in Example 45 to afford 0.025 g (23%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{21}O_5F_4Cl$ 560, found 578 and 580 ($M + NH_4$, 100%).

Example 58

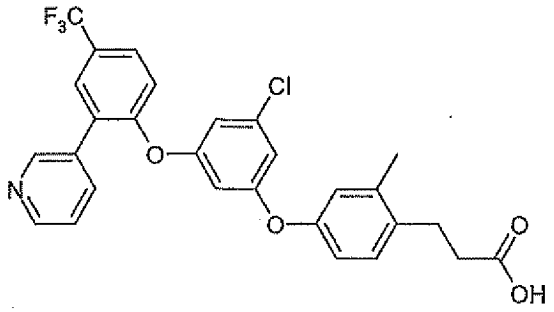
3-{4-[3-Chloro-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepare by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-chloro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 2-tributylstannyl pyridine as in Example 39 to afford 0.055 g (32%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{28}H_{21}NO_4F_3Cl$ 528.1190, found 528.1194.

Example 59

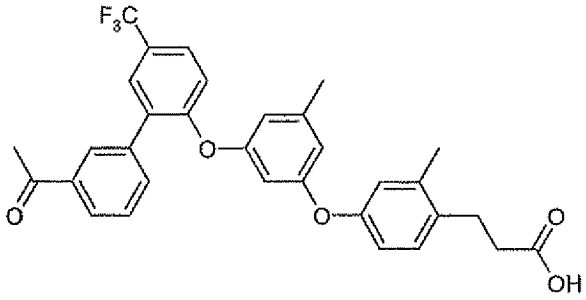
3-{4-[3-Chloro-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepare by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-chloro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with pyridine-3-boronic acid as in Example 38 to afford 0.067 g (63%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{28}H_{21}NO_4F_3Cl$ 528.1190, found 528.1186.

Example 60

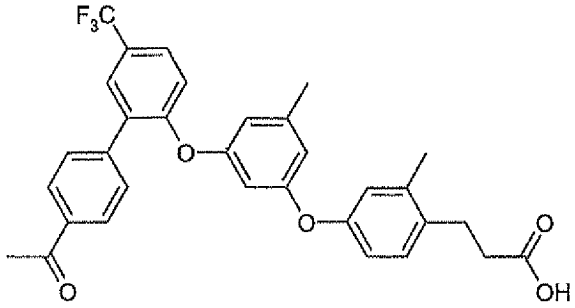
3-{4-[3-(3'-Acetyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



The compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester is reacted with 3-acetyl phenyl boronic acid as in Example 38 to afford 0.186 g (72%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{32}H_{28}O_5F_3$ 549.1888, found 549.1880.

Example 61

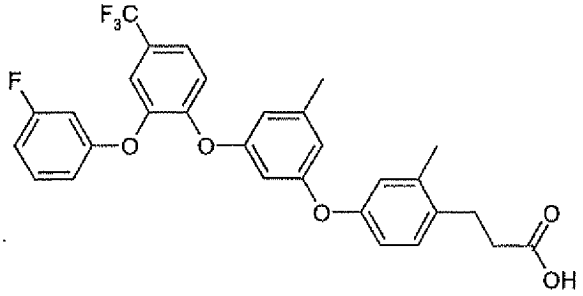
3-{4-[3-(4'-Acetyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



The compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester is reacted with 4-acetyl phenyl boronic acid as in Example 38 to afford 0.056 g (26%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{32}H_{28}O_5F_3$ 549.1888, found 549.1888.

Example 62

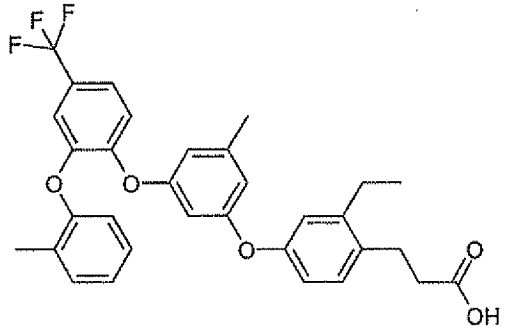
3 3-(4-{3-[2-(3-Fluoro-phenoxy)-4-trifluoromethyl-phenoxy]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid



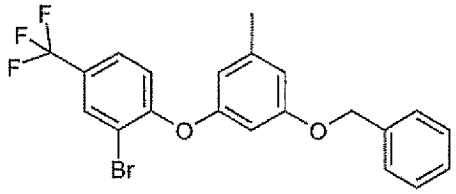
The compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester is reacted with 3-fluorophenol as in Example 45 to afford 0.106 g (40%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* mass calculated for $C_{30}H_{25}O_5F_4$ 541.1638, found 541.1625.

Example 63

3-{2-Ethyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



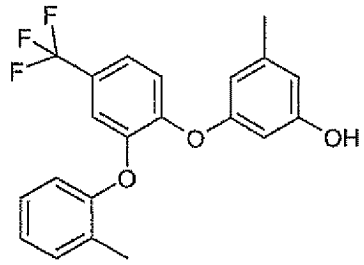
Step A



A mixture 3-benzyloxy-5-methyl-phenol (8.50 g, 39.7 mmol), 3-bromo-4-fluorobenzotrifluoride (9.64 g, 39.7 mmol) and 325 mesh potassium carbonate (6.58 g, 47.6 mmol) in dry DMSO (100 mL) is heated to 100 °C and stirred for 8 hours under N_2. The reaction is cooled and acidified with 1 N HCl. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 14.14 g (81%) product. R_f = 0.52 (4/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$).

Step B

3-Methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenol

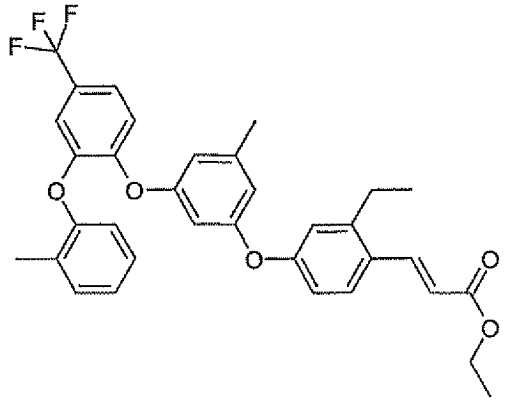


Compound of Step A (23.26 g, 53.2 mmol), o-cresol (17.26 g, 0.159 mol), cesium carbonate (51.99 g, 0.159 mol), and 2,2,6,6-tetramethyl-3,5-heptanedione (2.45 g, 13.3 mmol) in 1-methyl-2-pyrrolidinone (230 mL) is purged with N_2, and then copper (I) chloride (2.63 g, 26.6 mmol) is added. The reaction mixture is heated to 120 °C for 18 hours under N_2. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 25/1 hexanes/ethyl acetate to afford 23.69 g (96%) as a mixture of products that were carried on as is.

A mixture of 23.69 g of obtained above and 10% Pd/C (6.0 g) in ethyl acetate (200 mL) is purged with N_2 and then H_2, and the mixture is stirred under a H_2 balloon at rt. Upon completion of the reaction, the mixture is filtered through hyflo, and the solvent is removed *in vacuo* to afford crude product that is purified by flash chromatography using 96/4 $CHCl_3$/methyl *t*-butyl ether to afford 6.74 g (35%) of the title compound. R_f = 0.50 (9/1 $CHCl_3$/methyl *t*-butyl ether). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{21}H_{17}F_3O_3$ 374, found 375 (M +1, 100%).

Step C

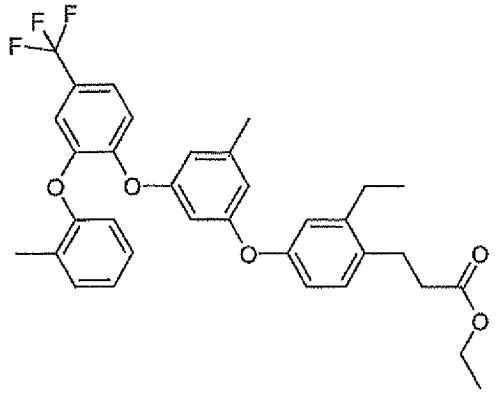
3-{2-Ethyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-acrylic acid ethyl ester



A 3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenol (3.20 g, 8.54 mmol), 3-(2-ethyl-4-fluoro-phenyl)-acrylic acid ethyl ester (1.90 g, 8.54 mmol) and 325 mesh potassium carbonate (1.42 g, 10.3 mmol), and $MgSO_4$ (1.03 g, 8.54 mmol) in dry DMSO (35 mL) is heated to 130 °C and stirred for 17 hours under N_2. The reaction is cooled and acidified with 1 N HCl. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 16/1 hexanes/ethyl acetate to afford 1.83 g (37%) of the title compound. $R_f = 0.37$ (4/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{34}H_{31}F_3O_5$ 576, found 577 (M + 1, 100%).

Step D

3-{2-Ethyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester



A mixture of 3-{2-ethyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)phenoxy]-phenyl}-acrylic acid ethyl ester (1.83 g, 3.17 mmol) and 10% Pd/C (1.80 g) in ethyl acetate (100 mL) is purged with N_2 then H_2 and then stirred under a H_2 balloon at rt for 5 hours. The mixture is filtered through hyflo, and the solvent is removed *in vacuo* to afford 1.77 g (97%) of the title compound. $R_f = 0.22$ (9/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{34}H_{33}F_3O_5$ 578, found 579 (M +1, 100%).

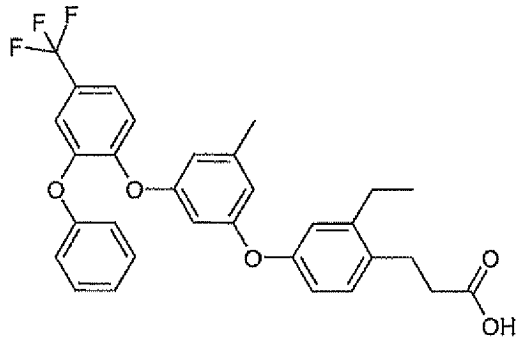
Step E

3-{2-Ethyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

A solution of 3-{2-ethyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid ethyl ester (1.77, 3.06 mmol) in ethanol (15 mL) is treated with 5 N NaOH (3 mL) and heated to reflux until saponification is completed. The mixture is cooled, and the solvent is removed *in vacuo* to afford a residue that is acidified with 1 N HCl. The mixture is diluted with water and extracted with ethyl acetate. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford 1.57 g (93%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{32}H_{30}O_5Cl$ 551.2045, found 551.2051.

Example 64

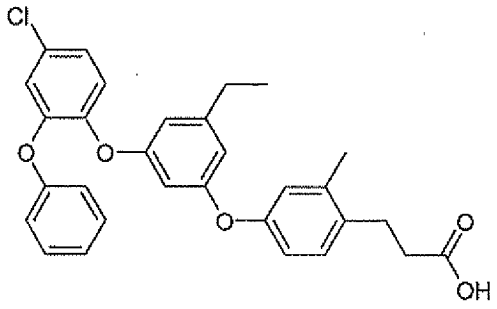
3-{2-Ethyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared by using the procedure and intermediates of Example 63. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{31}H_{28}O_5F_3$ 537.1888, found 537.1877.

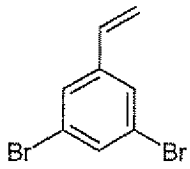
Example 65

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-ethyl-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

1,3-Dibromo-5-vinyl-benzene

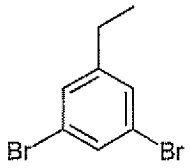


A solution of methyltriphenylphosphonium bromide (20.30 g, 56.8 mmol) in dry THF (50 mL) is cooled to 0 °C under N_2 and then treated with solid potassium *tert*-

butoxide (6.38 g, 56.8 mmol) in portions. The resultant yellow slurry is warmed to rt and stirred for 30 minutes. The mixture is cooled to -78 °C, and a solution of 3,5-dibromobenzaldehyde (10.0 g, 37.9 mmol) in THF (50 mL) is added dropwise. The reaction is warmed to rt and stirred for 1 hour. The mixture is poured into ice water containing 1 N HCl (56 mL) and then extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 10/1 hexanes/ethyl acetate to afford 4.56 g (46%) of the title compound. R_f = 0.64 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

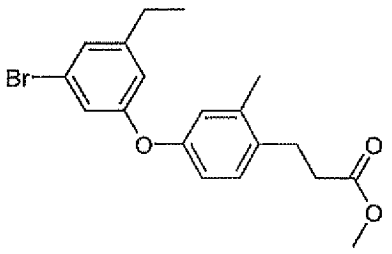
1,3-Dibromo-5-ethyl-benzene



A mixture of 1,3-dibromo-5-vinyl-benzene (4.55 g, 17.4 mmol) and 20% $Pd(OH)_2/C$ (2.0 g) in THF (60 mL) is purged with N_2 and then H_2, and the mixture is stirred under a H_2 balloon at rt for 5 hours. The mixture is filtered through hyflo, and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 15/1 hexanes/ethyl acetate to afford 3.38 g (74%) of the title compound. R_f = 0.63 (9/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step C

3-[4-(3-Bromo-5-ethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



Compound of 1,3-dibromo-5-ethyl-benzene is reacted with 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester as in Example 18 to afford 0.898 g (56%) of the title compound. R_f = 0.32 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS

(ES$^+$) *m/z* mass calculated for $C_{19}H_{21}O_3Br$ 376, found 377 and 379 (M + 1 and M + 3, 100%).

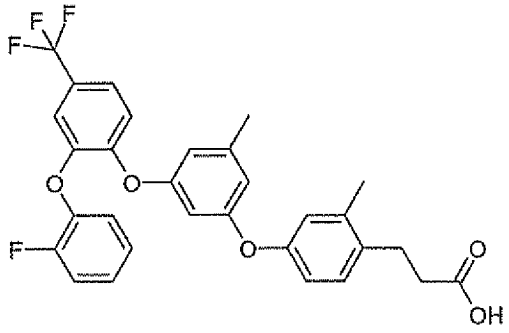
Step D

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-ethyl-phenoxy]-2-methyl-phenyl}-propionic acid

The compound of 3-[4-(3-bromo-5-ethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester is reacted with 4-chloro-2-phenoxy-phenol as in Example 18 to afford 0.237 g (36%) of the title compound after saponification. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES$^+$) *m/z* exact mass calculated for $C_{30}H_{28}O_5Cl$ 503.1625, found 503.1625.

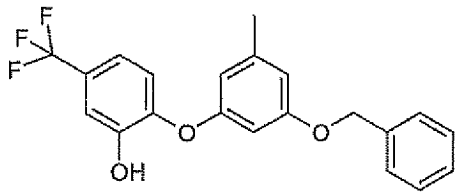
Example 66

3-(4-{3-[2-(2-Fluoro-phenoxy)-4-trifluoromethyl-phenoxy]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid



Step A

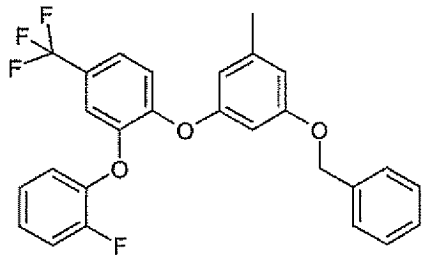
2-(3-Benzyloxy-5-methyl-phenoxy)-5-trifluoromethyl-phenol



A solution of Example 63, Step A intermediate (5.89 g, 13.5 mmol) in dry THF (60 mL) is cooled to -78 °C and treated with a 1.6 M solution of n-butyl lithium in hexanes (11.8 mL, 18.9 mmol) and stirred for 5 minutes at -78 °C under N_2. Trimethyl borate (1.96 g, 18.9 mmol) is added dropwise, and the mixture is warmed to 0 °C and

stirred for 20 minutes. The mixture is treated dropwise with a 30% aqueous solution of H_2O_2 (3.05 g, 26.9 mmol) and stirred for 15 minutes at 0 °C and warmed to rt and stirred for 1 hour. The reaction is acidified with 1 N HCl, diluted with ethyl acetate and then extracted with water and saturated aqueous $Na_2S_2O_3$. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 8/1 hexanes/ethyl acetate to afford 3.68 g (73%) of the title compound. R_f = 0.49 (2/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^-) *m/z* mass calculated for $C_{21}H_{16}O_3F_3$ 373.1052, found 373.1039.

Step B



A mixture of 2-(3-benzyloxy-5-methyl-phenoxy)-5-trifluoromethyl-phenol (0.42 g, 1.12 mmol), 1-bromo-2-fluorobenzene (0.39 g, 2.22 mmol), cesium carbonate (0.439 g, 1.35 mmol), and 2,2,6,6-tetramethyl-3,5-heptanedione (0.052 g, 0.282 mmol) and copper (I) chloride (0.056 g, 0.566 mmol) in toluene (8 mL) is heated to reflux for 18 hours under N_2. The reaction is cooled, and the mixture is acidified with 1 N HCl. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4) and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 15/1 hexanes/ethyl acetate to afford 0.094 g (18%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{27}H_{20}O_3F_4$ 468, found 469 (M + 1, 100%).

Step C

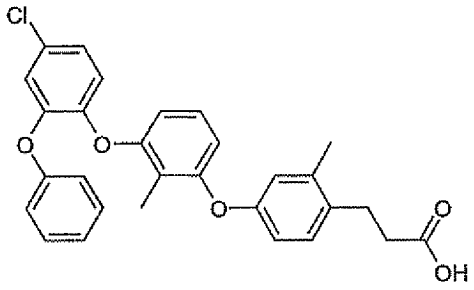
3-(4-{3-[2-(2-Fluoro-phenoxy)-4-trifluoromethyl-phenoxy]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid

Compound obtained in Step B is reacted with 3-(4-fluoro-2-methyl-phenyl)-acrylic acid ethyl ester (Example 22) as in Example 63 to afford 0.070 g (19%) of

the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{24}O_5F$ 540, found 541 (M + 1, 100%).

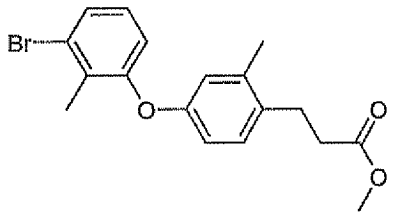
Example 67

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-2-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



Step A

3-[4-(3-Bromo-2-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



A mixture of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (2.0 g, 10.3 mmol), 2,6-dibromotoluene (7.72 g, 30.9 mmol), cesium carbonate (4.03 g, 12.4 mmol), and 2,2,6,6-tetramethyl-3,5-heptanedione (0.47 g, 2.55 mmol) in 1-methyl-2-pyrrolidinone (20 mL) is purged with N_2, and then copper (I) chloride (0.51 g, 5.15 mmol) is added. The reaction is heated to 120 °C for 17 hours under N_2, and then cooled and quenched with 1 N HCl (50 mL). The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 2.92 g (78%) of the title compound. R_f = 0.35 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{18}H_{19}O_3Br$ 362, found 363 and 365 (M +1 and M + 3, 100%).

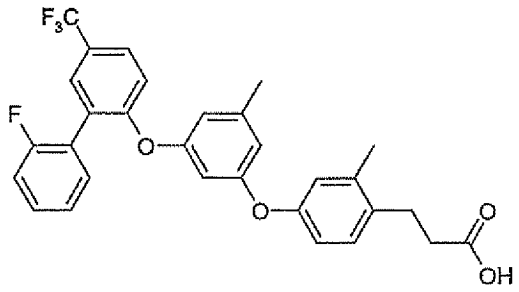
Step B

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-2-methyl-phenoxy]-2-methyl-phenyl}-propionic acid

3-[4-(3-bromo-2-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester is reacted with 4-chloro-2-phenoxy-phenol as in Example 18 to afford 0.031 g (9%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{29}H_{25}O_5Cl$ 488, found 489 and 491 (M + 1 and M + 3, 100%).

Example 68

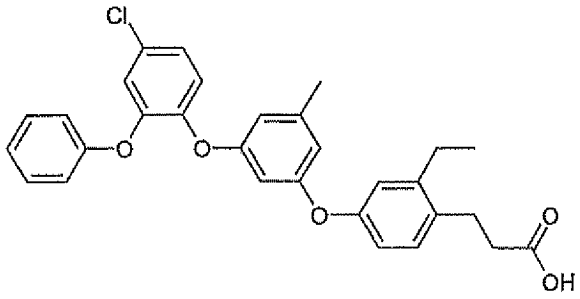
3-{4-[3-(2'-Fluoro-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



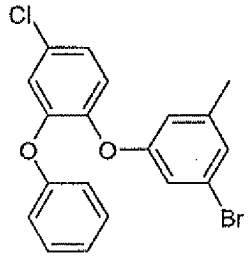
The tile compound is prepared by reacting 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester with 2-fluorobenzene boronic acid as in Example 38 to afford 0.216 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{30}H_{25}O_4F_4$ 525.1689, found 525.1675.

Example 69

3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid



Step A



A mixture of 4-chloro-2-phenoxy-phenol (6.46 g, 29.3 mmol), 3,5-dibromotoluene (21.95 g, 87.8 mmol), cesium carbonate (11.45 g, 35.1 mmol), and 2,2,6,6-tetramethyl-3,5-heptanedione (1.35 g, 7.33 mmol) in 1-methyl-2-pyrrolidinone (65 mL) is purged with N_2, and copper (I) chloride (1.45 g, 14.6 mmol) is added. The reaction heated to 120 °C for 20 hours under N_2. The reaction is cooled and quenched with 1 N HCl (20 mL). The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 100% hexanes to afford 7.84 g (69%) of the title compound. R_f = 0.49 (9/1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

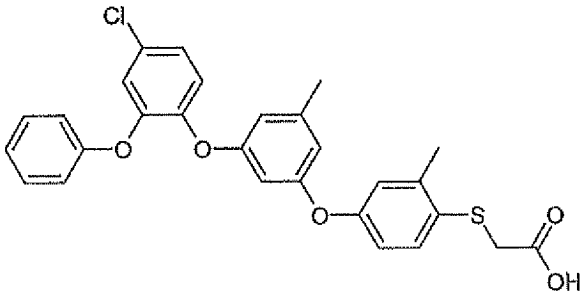
3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid

A mixture of compound obtained in Step A (0.30 g, 0.770 mmol), 3-(2-ethyl-4-hydroxy-phenyl)-propionic acid ethyl ester (0.170 g, 0.77 mmol), cesium carbonate (0.301 g, 0.924 mmol), copper (I) chloride (0.038 g, 0.384 mmol) and 2,2,6,6-

tetramethyl-3,5-heptanedione (0.035 g, 0.190 mmol) in 1-methyl-2-pyrrolidinone (6 mL) is heated to 120 °C for 17 hours under N_2. The reaction is treated with aqueous 5 N NaOH (3 mL) and then cooled to rt and stirred until saponification is completed. The reaction is acidified with aqueous 1 N HCl, and the resultant mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is purified by preparative HPLC to afford 0.014 g (4%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{27}O_5Cl$ 502, found 503, and 505 (M +1 and M + 3, 100%).

Example 70

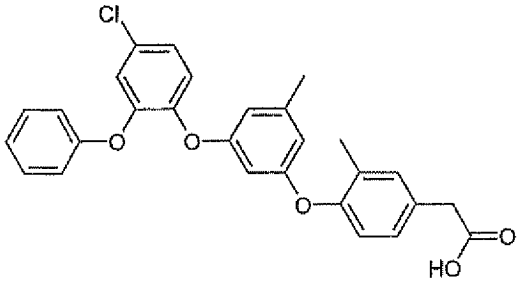
{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-methyl-phenylsulfanyl}-acetic acid



The title compound is prepared by reacting the compound of Example 69, Step A with (4-hydroxy-2-methyl-phenylsulfanyl)-acetic acid ethyl ester to afford 0.037 g (11%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{23}O_5SCl$ 506, found 507 and 509 (M + 1 and M + 3, 100%).

Example 71

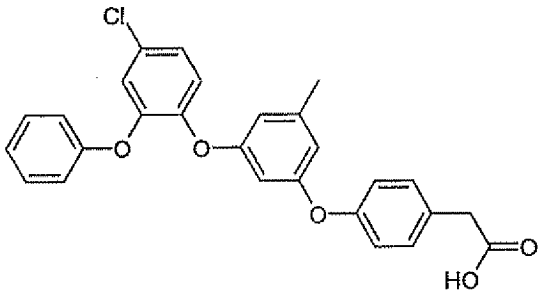
{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-3-methyl-phenyl}-acetic acid



The title compound is prepared by reacting the compound of Example 69, Step A with (4-hydroxy-3-methyl-phenyl)-acetic acid methyl ester to afford 0.019 g (6%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{23}O_5Cl$ 474, found 475 and 477 (M + 1 and M + 3, 100%).

Example 72

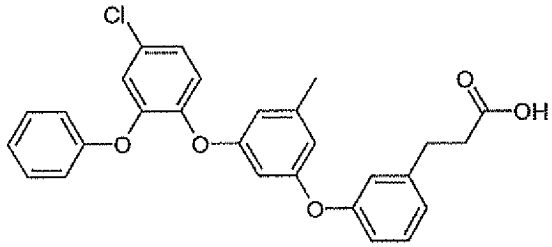
{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-phenyl}-acetic acid



The title compound is prepared by reacting the compound of Example 69, Step A with (4-hydroxy-phenyl)-acetic acid methyl ester to afford 0.034 g (10%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{27}H_{21}O_5Cl$ 460, found 461 and 463 (M + 1 and M + 3, 100%).

Example 73

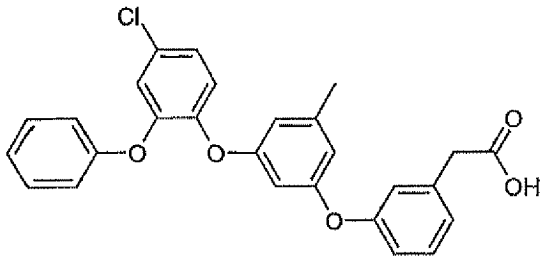
3-{3-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-phenyl}-propionic acid



The title compound is prepared by reacting the compound of Example 69, Step A with 3-(3-hydroxy-phenyl)-propionic acid methyl ester to afford 0.011 g (4%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{28}H_{23}O_5Cl$ 474, found 475 and 475 (M + 1 and M + 3, 100%).

Example 74

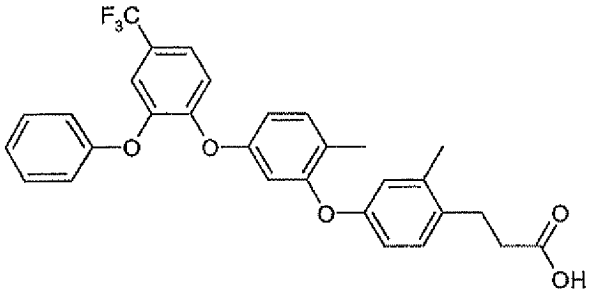
{3-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-phenyl}-acetic acid



The title compound is prepared by reacting the compound of Example 69, Step A with (3-hydroxy-phenyl)-acetic acid methyl ester to afford 0.070 g (21%). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{27}H_{21}O_5Cl$ 460, found 461 and 463 (M + 1 and M + 3, 100%).

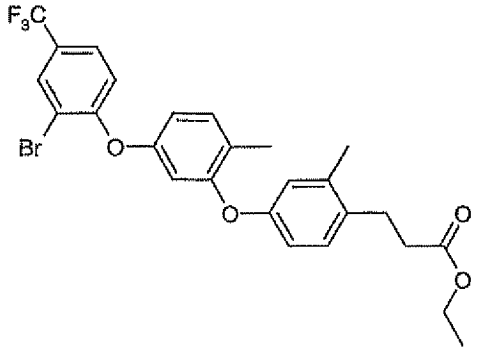
Example 75

3-{2-Methyl-4-[2-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

3-{4-[5-(2-Bromo-4-trifluoromethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester



A mixture of 3-[4-(5-hydroxy-2-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester (Example 84, Step D) (0.46 g, 1.46 mmol), 3-bromo-4-fluorobenzotrifluoride (0.35 g, 1.45 mmol) and 325 mesh potassium carbonate (0.21 g, 1.52 mmol) in dry DMSO (10 mL) is heated to 100 °C and stirred for 6 hours under N_2. The reaction is cooled and acidified with 1 N HCl. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 0.633 g (81%) of the title compound. R_f = 0.38 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{26}H_{24}O_4F_3Br$ 536, found 554 and 556 (M + NH_4, 100%).

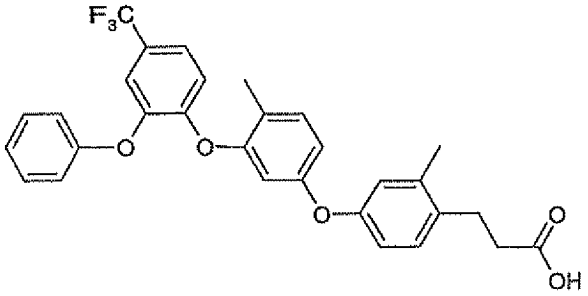
Step B

3-{2-Methyl-4-[2-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

3-{4-[5-(2-Bromo-4-trifluoromethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester is reacted with phenol as in Example 45 to afford 0.168 g (33%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{30}H_{26}O_5F_3$ 523.1732, found 523.1736.

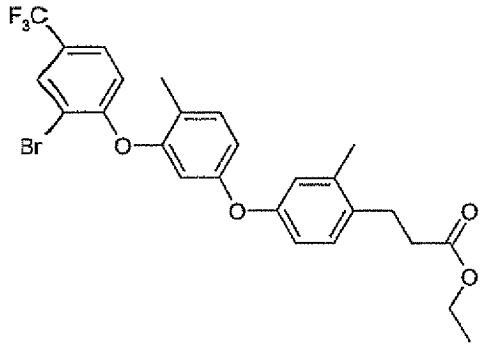
Example 76

3-{2-Methyl-4-[4-methyl-3-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-4-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester



A mixture of 3-[4-(3-hydroxy-4-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester (Example 82, Step J) (1.05 g, 3.34 mmol), 3-bromo-4-fluorobenzotrifluoride (0.81 g, 3.34 mmol) and 325 mesh potassium carbonate (0.55 g, 3.97 mmol) in dry DMSO (1 5 mL) is heated to 100 °C and stirred for 6 hours under N_2. The reaction is cooled and acidified with 1 N HCl. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 1.57 g (88%) of the title compound. $R_f = 0.38$ (4/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{26}H_{24}O_4F_3Br$ 536, found 554 and 556 (M + NH_4, 100%).

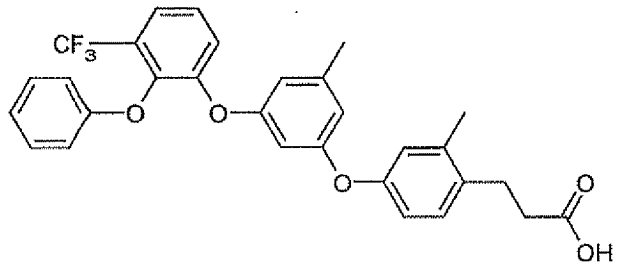
Step B

3-{2-Methyl-4-[4-methyl-3-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

The compound of 3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-4-methyl-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester is reacted with phenol as in Example 45 to afford 0.256 g (57%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); HRMS (ES^+) *m/z* exact mass calculated for $C_{30}H_{26}O_5F_3$ 523.1732, found 523.1749.

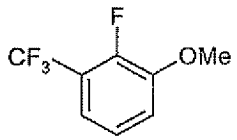
Example 77

3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-3-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

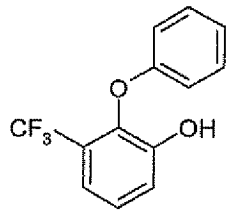
2-Fluoro-3-methoxybenzotrifluoride



A mixture of 2-fluoro-3-(trifluoromethyl)-phenol (4.87 g, 27.04 mmol) and iodomethane (4.60 g, 32.4 mmol) in acetone (50 mL) is cooled to 0 °C and then 325 mesh potassium carbonate (4.48 g, 32.4 mmol) is added. The reaction is warmed to rt and stirred for 17 hours under N_2. The reaction filtered to remove the solids, and the filtrate is acidified with 1 N HCl. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford 4.76 g (91%) of 2-fluoro-3-methoxybenzotrifluoride that is utilized without purification. R_f = 0.35 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

2-Phenoxy-3-trifluoromethyl-phenol



A mixture of 2-fluoro-3-methoxybenzotrifluoride (4.76 g, 24.5 mmol), phenol (2.30 g, 24.4 mmol) and 325 mesh potassium carbonate (4.07 g, 29.4 mmol) in dry DMSO (50 mL) is heated to 130 °C and stirred 17 hours under N_2. The reaction filtered to remove the solids, and the filtrate is acidified with 1 N HCl. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4) and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 12/1 hexanes/ethyl acetate to afford 3.47 g (53%) of 2-phenoxy-3-trifluoromethyl-anisole (R_f = 0.30 (4/1 hexanes/EtOAc) that is contaminated with starting 2-fluoro-1-methoxy-3-trifluoromethyl-benzene.

A –78 °C solution of the crude 2-phenoxy-3-trifluoromethyl-anisole (3.47g, 12.9 mmol) in CH_2Cl_2 (35 mL) is treated with BBr_3 (12.99 g, 51.8 mmol), and the mixture is warmed to 0 °C and stirred for 1.5 h under N_2. The reaction is poured into ice water and then extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude material that is absorbed on silica gel and columned with 96/4 chloroform/methyl *tert*-butyl ether to afford 1.51 g (24%) of 2-phenoxy-3-trifluoromethyl-phenol. R_f = 0.34 (96/4 chloroform/methyl *tert*-butyl ether). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES-$^+$) *m/z* mass calculated for $C_{13}H_9O_2F_3$ 254, found 253 (M+1, 100%).

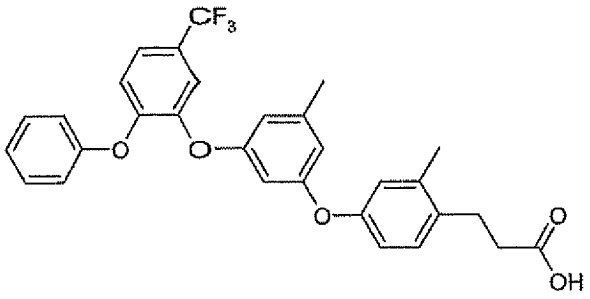
Step C

3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-3-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

2-Phenoxy-3-trifluoromethyl-phenol is reacted with 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester as in Example 18 to afford 0.125 g (17%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{25}O_5F_3$ 522, found 523 (M + 1, 100%).

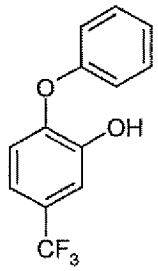
Example 78

3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-5-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

2-Phenoxy-5-trifluoromethyl-phenol



A mixture of 4-fluoro-3-methoxybenzotrifluoride (5.26 g, 28.9 mmol), phenol (2.71 g, 28.8 mmol) and 325 mesh potassium carbonate (4.79 g, 34.7 mmol) in dry DMSO (50 mL) is heated to 130 °C and stirred for 17 hours under N_2. The reaction is filtered, and the filtrate is acidified with 1 N HCl. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 15/1 hexanes/ethyl acetate to afford 3.79 g (49%) of the title compound (R_f = 0.47 (4/1 hexanes/EtOAc) that is contaminated with starting 4-fluoro-3-methoxybenzotrifluoride.

A –78 °C solution of the crude 2-phenoxy-5-trifluoromethyl-anisole (3.79 g, 14.1 mmol) in CH_2Cl_2 (38 mL) is treated with BBr_3 (14.04 g, 56.1 mmol) and then warmed to 0 °C. The mixture is stirred for 1.5 h under N_2, poured into ice water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude material that is absorbed on silica gel and columned with 6/1

hexanes/ethyl acetate to afford 1.29 g (18%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES-$^+$) *m/z* mass calculated for $C_{13}H_9O_2F_3$ 254, found 253 (M + 1, 100%).

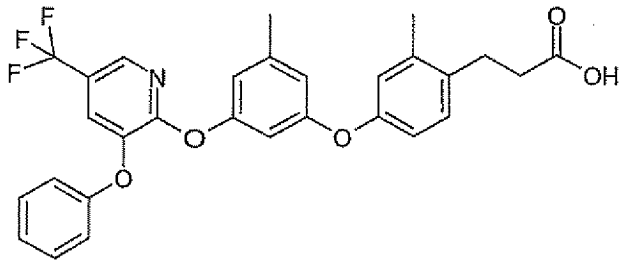
Step B

3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-5-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

The compound of 2-phenoxy-5-trifluoromethyl-phenol is reacted with 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester as in Example 18 to afford 0.262 g (34%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{30}H_{25}O_5F_3$ 522, found 523 (M + 1, 100%).

Example 79

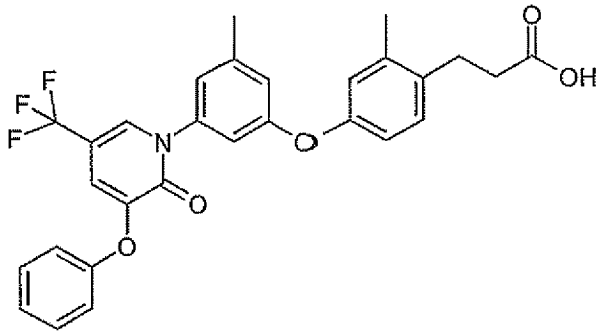
3-{2-Methyl-4-[3-methyl-5-(3-phenoxy-5-trifluoromethyl-pyridin-2-yloxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 8 by using 3-phenoxy-5-trifluoromethyl-pyridin-2-ol and 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford 32 mg (6%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{24}O_5NF_3$ 523, found 524 (M + 1, 100%).

Example 80

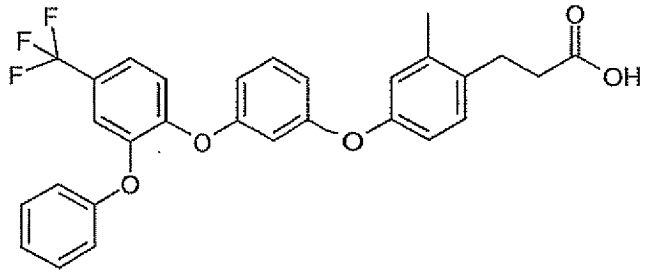
3-{2-Methyl-4-[3-methyl-5-(2-oxo-3-phenoxy-5-trifluoromethyl-2H-pyridin-1-yl)-phenoxy]-phenyl} -propionic acid



The title compound is prepared according to Example 8 by using 3-phenoxy-5-trifluoromethyl-pyridin-2-ol and 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford 37 mg (7%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{24}O_5NF_3$ 523, found 524 (M + 1, 100%).

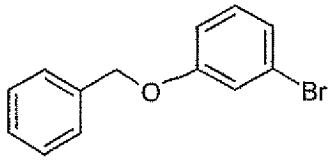
Example 81

3-{2-Methyl-4-[3-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

3-Benzyloxy-1-bromobenzene

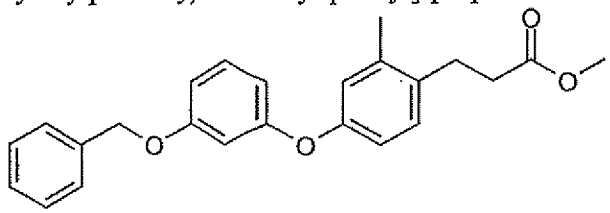


A mixture of 3-bromophenol (10.0 g, 57.8 mmol) and 325 mesh potassium carbonate (8.79 g, 63.6 mmol) in DMF (100 mL) is treated dropwise with benzyl bromide (9.89 g, 57.8 mmol) and then stirred 20 hours at rt under N_2. The reaction is filtered, and

the filtrate is acidified with 1 N HCl. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 10/1 hexanes/ethyl acetate to afford 14.55 g (96%) of the titled compound. R_f = 0.86 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

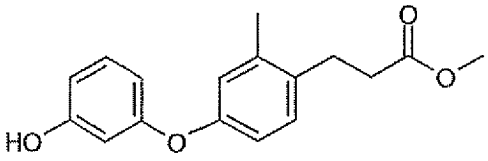
3-[4-(3-Benzyloxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



A mixture of 3-benzyloxy-1-bromobenzene (14.53 g, 55.2 mmol), 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (10.72 g, 55.2 mmol), cesium carbonate (21.59 g, 66.3 mmol), and 2,2,6,6-tetramethyl-3,5-heptanedione (2.54 g, 13.8 mmol) in 1-methyl-2-pyrrolidinone (100 mL) is purged with N_2 and then copper (I) chloride (2.73 g, 27.6 mmol) is added. The reaction mixture is heated to 120 °C for 18 hours under N_2. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using a gradient of 19/1 to 9/1 hexanes/ethyl acetate to afford 10.54 g (51%) of the titled compound. R_f = 0.53 (100% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{24}H_{24}O_4$ 376, found 377 (M + 1, 100%).

Step C

3-[4-(3-Hydroxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

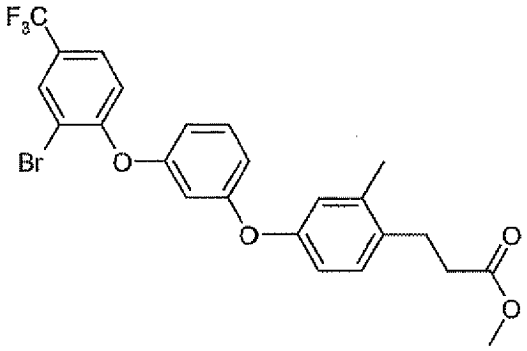


A mixture of 3-[4-(3-benzyloxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (10.54 g, 28.0 mmol) and 10% Pd/C (5 g) in ethyl acetate (150 mL) is purged with N_2 and then H_2. The mixture is stirred under a hydrogen balloon. Upon completion, the mixture is filtered through hyflo, and the solvent is removed *in vacuo* to

afford 8.18 g (100%) of the titled compound. R_f = 0.59 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{17}H_{18}O_4$ 286, found 287 (M + 1, 100%).

Step D

3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester



A mixture of 3-[4-(3-hydroxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (8.18 g, 28.6 mmol), 3-bromo-4-fluorobenzotrifluoride (6.80 g, 28.0 mmol) and 325 mesh potassium carbonate (4.64 g, 33.68 mmol) in dry DMSO (80 mL) is heated to 100 °C and stirred 6 hours under N_2. The reaction is cooled and acidified with 1 N HCl. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4, and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 15/1 hexanes/ethyl acetate to afford 11.74 g (81%) of the titled compound. R_f = 0.76 (9/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{24}H_{20}O_4F_3Br$ 509, found 526 and 528 (M + NH_4, 100%).

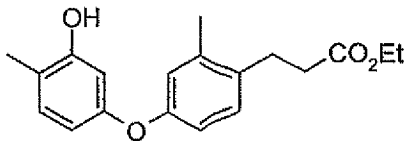
Step E

3-{2-Methyl-4-[3-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

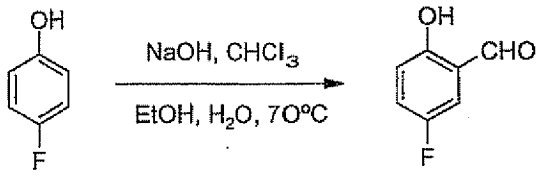
The title compound is prepare by reacting the compound of 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester with *o*-cresol as in Example 45 to afford 0.229 g (21%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{25}O_5F_3$ 522, found 523 (M + 1, 100%).

Example 82

3-[4-(3-hydroxy-4-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester

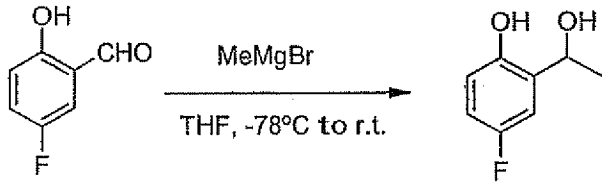


Step A



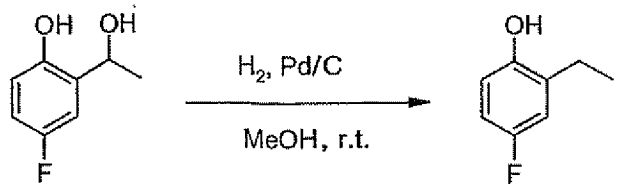
A solution of NaOH (78 g, 1950 mmol) in H_2O (400 mL) is added to a solution of 4-fluorophenol (50 g, 446.43 mmol) in a mixture of H_2O (200 mL) and EtOH (150 mL). After the mixture is warmed to 70°C, $CHCl_3$ (110 mL) is added dropwise (addition funnel, about 2 h), and the mixture is stirred at this temperature overnight (c.a. 16 h). It is allowed to reach r.t. and acidified with HCl (3M). The reaction is partitioned between brine and CH_2Cl_2, and the organic layer is dried, filtered and concentrated. The crude residue is flash chromatographed on SiO_2 (3% EtOAc/hexanes) to afford 13.6 of the title compound (22%, white solid).

Step B



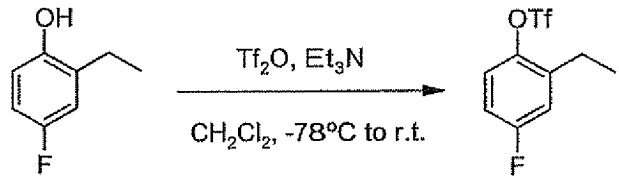
MeMgBr (10 mL, 3 M solution in Et_2O) is added to a –78 °C cooled solution of aldehyde (2 g, 14.285 mmol) in THF (30 mL). The mixture is allowed to reach r.t., stirred for 30 min. and poured into brine. It is acidified with diluted HCl and extracted with EtOAc. The organic layer is dried, filtered and concentrated, to give a crude residue that is purified by flash chromatography on SiO_2 (10-15% EtOAc/hexanes) to afford 2.1 g of the addition product (94%, colorless oil).

Step C



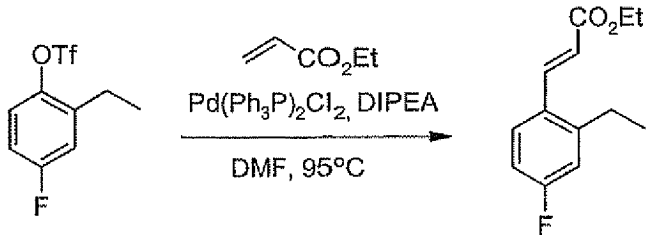
A mixture of Pd/C (1.2 g, 10% Pd on activated carbon, 1.128 mmol) and the hydroxyphenol (11.6 g, 74.35 mmol) in MeOH (100 mL) is stirred under H_2 atmosphere (balloon) for 7 h. The mixture is filtered through Celite (EtOAc washings), and the solvent is removed in a rotatory evaporator. The crude residue is flash chromatographed on SiO_2 (10-15% EtOAc/hexanes) to afford 10.25 g of 2-ethyl-4-fluorophenol (99%, colorless oil).

Step D



Triflic anhydride (13.4 mL, 79.65 mmol) is added to a –78°C cooled solution of ethylfluorophenol (10.2 g, 72.85 mmol) and Et_3N (20 mL, 143.38 mmol) in CH_2Cl_2 (100 mL). The mixture is allowed to reach r.t., poured into brine, and extracted with CH_2Cl_2. The organic layer is washed with HCl (3%) and brine, dried, filtered and concentrated to give a crude residue that is flash chromatographed on SiO_2 (3% EtOAc/hexanes) affording 13.9 g of the desired triflate (70 %, colorless oil).

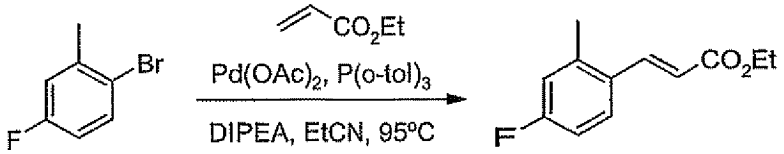
Step E



A mixture of ethyl acrylate (25 mL, 277.6 mmol), DIPEA (25 mL, 143.52 mmol), $Pd(Ph_3P)_2Cl_2$ (2 g, 2.85 mmol) and ehtylfluorotriflate (10 g, 36.764 mmol) in DMF (60 mL) is warmed to 95°C and stirred at this temperature for 70 h. The mixture is allowed to reach r.t., filtered through Celite (EtOAc washings) and partitioned between

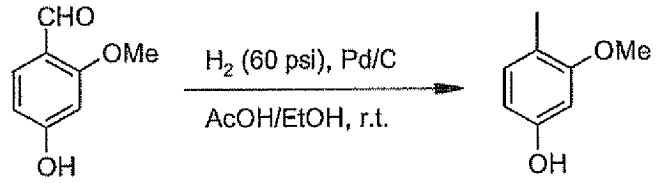
EtOAc and brine. The organic layer is washed with HCl (3%), dried, filtered and concentrated to give a crude residue that is flash chromatographed on SiO_2 (1% EtOAc/hexanes) affording 4.6 g of the title compound and 3.5 g of unreacted starting triflate (56%, colorless oil).

Step F



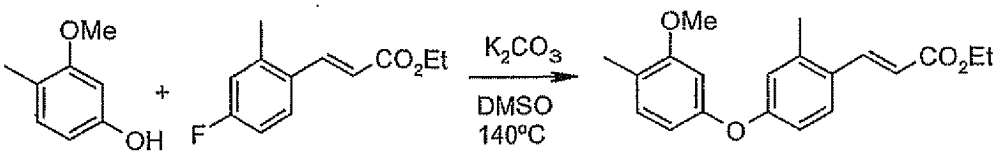
A mixture of 4-bromo-3-methylfluorobenzene (8 g, 42.32 mmol), ethyl acrylate (12 mL, 133.25 mmol), $Pd(OAc)_2$ (960 mg, 4.276 mmol), $P(o\text{-}tol)_3$ (2.56 g, 8.41 mmol) and DIPEA (12 mL, 68.89 mmol) in EtCN (100 mL) is warmed to 95°C, and stirred at this temperature for 7 h. The reaction is allowed to reach r.t., filtered through Celite, and partitioned between EtOAc and HCl (3%). The organic layer is dried, filtered and concentrated to give a crude residue that is flash chromatographed on SiO_2 (2% EtOAc/hexanes) affording 8.1 g of the Heck product (92%, colorless oil).

Step G



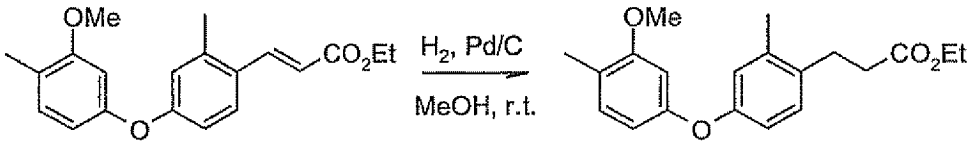
A mixture of Pd/C (1 g, 10% Pd on activated C, 0.94 mmol) and the aldehyde (3.9 g, 25.658 mmol) in EtOH (75 mL) and glacial AcOH (15 mL) is stirred at r.t. under H_2 atmosphere (60 psi) overnight (c.a. 14 h). The mixture is filtered through Celite, and the solvent is removed in a rotatory evaporator. The crude residue is purified by flash chromatography on SiO_2 (15% EtOAc/hexanes) to afford 3.14 g of 4-methyl-3-methoxyphenol (89%, colorless oil).

Step H



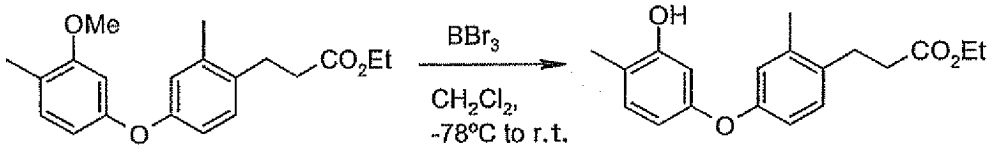
K_2CO_3 (3 g, 21.7 mmol) is added to a solution of the phenol (2.0 g, 14.5 mmol) and the fluoride (3.6 g, 17.3 mmol) in DMSO (40 mL). The mixture is warmed to 140°C and stirred at this temperature overnight (c.a. 16 h). The mixture is allowed to reach r.t. and partitioned between EtOAc and HCl (3%). The organic layer is dried, filtered and concentrated to give a crude residue that is flash chromatographed on SiO_2 (2-3% EtOAc/hexanes) affording 2.42 g of the coupling product (51%, colorless oil).

Step I



A mixture of Pd/C (500 mg, 10% Pd on activated C, 0.47 mmol) and the unsaturated ester (2.3 g, 7.055 mmol) and MeOH (35 mL) is stirred at r.t. under H_2 atmosphere (balloon) for 1 h. The reaction is filtered through Celite, and the solvent is removed in a rotatory evaporator. The crude residue is flash chromatographed on SiO_2 (4% EtOAc/hexanes) to afford 2.1 g of the saturated ester (91%, colorless oil).

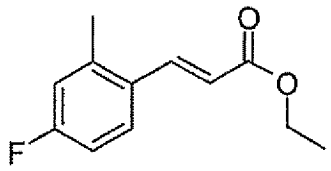
Step J



BBr_3 (8 mL, 1M solution in CH_2Cl_2) is added to a -78°C cooled solution of the methoxyphenolether (2.0 g, 6.1 mmol) in CH_2Cl_2 (30 mL), and the mixture is allowed to reach r.t. After 15 min., it is poured into brine and extracted with CH_2Cl_2. The organic layer is washed with $NaHCO_3$ (sat) and H_2O, and then dried, filtered and concentrated. The resulting crude residue is flash chromatographed on SiO_2 (5-7% EtOAc/hexanes) to afford 1.15 g of the title compound (60%, white solid).

Example 83

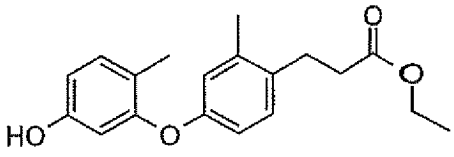
3-(4-Fluoro-2-methyl-phenyl)-acrylic acid ethyl ester



A mixture of 1-bromo-4-fluoro-2-methyl-benzene (5.00 g, 26.45 mmol), palladium acetate (0.59 g, 2.64 mmol), tri-o-tolylphosphine (1.61 g, 5.29 mmol), DIPEA (13.8 mL, 79.35 mmol) and ethyl acrylate (3.34 mL, 105.80 mmol) in propionitrile (106 mL) is stirred at 90 °C under nitrogen overnight. The mixture is ed off through Celite and washed with ethyl acetate. The mixture is concentrated under reduced pressure, purified by flash chromatography by eluting with hexane: ethyl acetate 10:1 to afford the title compound (5.50 g, 99 %). Rf = 0.49 (hexane: ethyl acetate 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ1.33 (t, 3 H, *J*= 7.3 Hz), 2.41 (s, 3 H), 4.26 (q, 2 H, *J*= 7.3 Hz), 6.28 (d, 1 H, *J*= 16.0 Hz), 6.88-6.91 (m, 2 H), 7.48-7.53 (m, 1 H), 7.88 (d, 1 H, *J*= 15.8 Hz).

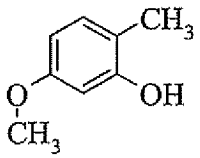
Example 84

3-[4-(5-Hydroxy-2-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester



Step A

5-Methoxy-2-methyl-phenol

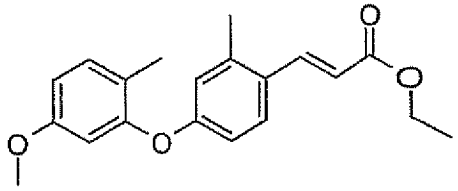


A solution of 2-hydroxy-4-methoxy-benzaldehyde (5.00 g, 32.86 mmol) and palladium under carbon (10 %) (3.50 g, 3.28 mmol) in ethanol (32 mL) and acetic acid (3 mL) is stirred under 60 psi of hydrogen. After stirring overnight, the mixture is filtered off through Celite and washed with methanol. The mixture is concentrated under reduced pressure, and purified by flash chromatography by eluting with hexane: ethyl

acetate 2:1 to afford the title compound (3.96 g, 87 %). Rf = 0.58 (hexane: ethyl acetate 2:1). δ^1H NMR (300 MHz, $CDCl_3$): 2.18 (s, 3 H), 3.75 (s, 3 H), 6.42 (m, 2 H), 7.00(d, 1 H, *J*= 8.9 Hz).

Step B

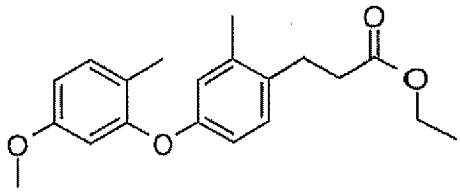
3-[4-(5-Methoxy-2-methyl-phenoxy)-2-methyl-phenyl]-acrylic acid ethyl ester



The compounds of 5-methoxy-2-methyl-phenol (1.46 g, 9.60 mmol), 3-(4-fluoro-2-methyl-phenyl)-acrylic acid ethyl ester (1.00 g, 4.80 mmol), potassium carbonate (1.33 g, 9.60 mmol) are dissolved in dimethylsulfoxide (12 mL) under nitrogen, and the mixture is stirred overnight at 140 °C. HCl 10 % is added, and the mixture is extracted with diethyl ether. The organic layer is washed with water, dried (Na_2SO_4) and filtered, and then the solvent is evaporated in vacuo. Purification by flash chromatography by eluting with hexane: ethyl acetate 10:1 to afford the title compound (0.74 g, 47 %). Rf = 0.44 (hexane: ethyl acetate 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ1.34 (t, 3 H, *J*= 7.3 Hz), 2.13 (s, 3 H), 2.40 (s, 3 H), 3.74 (s, 3 H), 4.26 (q, 2 H, *J*= 7.1 Hz), 6.28 (d, 1 H, *J*= 15.9 Hz), 6.53 (d, 1 H, *J*= 2.4 Hz), 6.66-6.73 (m, 3 H), 7.15 (d, 1 H, *J*= 8.3 Hz), 7.51 (d, 1 H, *J*= 8.3 Hz), 7.93 (d, 1 H, *J*= 16.0 Hz).

Step C

3-[4-(5-Methoxy-2-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester



A solution of 3-[4-(5-methoxy-2-methyl-phenoxy)-2-methyl-phenyl]-acrylic acid ethyl ester (1.18 g, 3.63 mmol) and palladium under carbon (10 %) (0.39 g, 0.36 mmol) in ethanol (20 mL) and acetic acid (2 mL) is stirred under 1 atm of hydrogen. After stirring overnight, the mixture is filtered off through Celite and washed with methanol. The mixture is concentrated under reduced pressure and purified by flash

chromatography by eluting with hexane: ethyl acetate 5:1 to afford the title compound (1.02 g, 85 %). Rf = 0.42 (hexane: ethyl acetate 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ1.26 (t, 3 H, *J*= 6.9 Hz), 2.16 (s, 3 H), 2.28 (s, 3 H), 2.56 (t, 2 H, *J*= 7.3 Hz), 2.90 (t, 2 H, *J*= 7.3 Hz), 3.72 (s, 3 H), 4.17 (q, 2 H, *J*= 6.9 Hz), 6.45 (d, 1 H, *J*= 2.4 Hz), 6.62 (dd, 1 H, *J*= 2.8, 8.5 Hz), 6.67 (dd, 1 H, *J*= 2.4, 8.1 Hz), 6.74 (d, 1 H, *J*= 2.4 Hz), 7.06 (d, 1 H, *J*= 8.1 Hz), 7.13 (d, 1 H, *J*= 8.1 Hz).

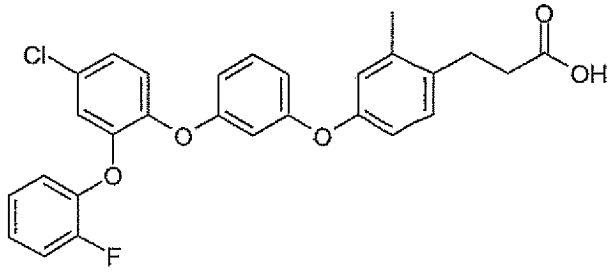
Step D

3-[4-(5-Hydroxy-2-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester

The compound of 3-[4-(5-Methoxy-2-methyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester (1.02 g, 3.10 mmol) is dissolved in DCM (15 mL) under nitrogen at -78 °C, and BBr_3 (1M, CH_2Cl_2) (4.64 mL, 4.64 mmol) is added. The mixture is stirred at that temperature for 10 minutes and the bath is removed. The mixture is stirred at rt for 2 h, and water is added. The mixture is neutralized to pH=7 with NaOH (10 %). The mixture is extracted with DCM. The organic layer is dried with Na_2SO_4 and filtered, and then the solvent is evaporated in vacuo. Purification by flash chromatography by eluting with hexane: ethyl acetate 5:1 to afford the title compound (0.48 g, 50 %). Rf = 0.13 (hexane: ethyl acetate 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ1.26 (t, 3 H, *J*= 7.3 Hz), 2.16 (s, 3 H), 2.26 (s, 3 H), 2.57 (t, 2 H, *J*= 7.3 Hz), 2.89 (t, 2 H, *J*= 7.5 Hz), 4.15 (q, 2 H, *J*= 7.3 Hz), 6.44 (d, 1 H, *J*= 2.4 Hz), 6.58 (dd, 1 H, *J*= 2.4, 8.1 Hz), 6.68 (dd, 1 H, *J*= 2.4, 8.3 Hz), 6.75 (d, 1 H, *J*= 2.2 Hz), 6.92 (s, 1 H), 7.04 (t, 2 H, *J*= 8.1 Hz).

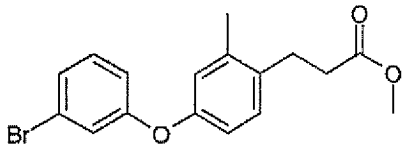
Example 85

3-(4-{3-[4-Chloro-2-(2-fluoro-phenoxy)-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid



Step A

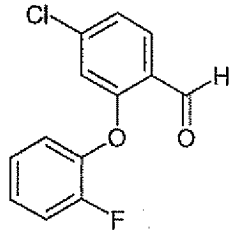
3-[4-(3-Bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



A solution of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (5.0 g, 26 mmol), 1-bromo-3-iodobenzene (21.9 g, 77 mmol), copper(I) chloride (1.3 g, 13 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (1.3 mL, 6.5 mmol), and cesium carbonate (12.7 g, 39 mmol) in NMP (100 mL) is heated to 120 °C. The reaction is stirred overnight, and then is cooled to room temperature. The reaction is then quenched with 1N aqueous hydrochloric acid and extracted with ethyl ether. The organic is washed with brine, dried over sodium sulfate, filtered, and the solvent is removed. The crude is purified by silica gel column chromatography using 9/1 hexanes/ethyl acetate to elute the pure product. The solvent is removed to afford about 7.86 g (87%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{17}H_{17}BrO_3$ 348, found 349 (M + 1, 100%).

Step B

4-Chloro-2-(2-fluoro-phenoxy)-benzaldehyde

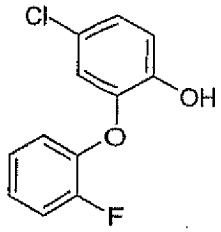


A solution of 4-chloro-2-fluorobenzaldehyde (1 .0 g, 6.3 mmol) and 2-fluorophenol (0.78 g, 6.9 mmol) in DMSO (10 mL) is treated with potassium carbonate (1.04 g, 7.6 mmol). The reaction is heated to 100 °C and stirred overnight. The reaction is cooled to room temperature and quenched with 1N aqueous hydrochloric acid to pH=6. The aqueous is extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate, filtered, and the solvent is removed. The crude is purified by silica gel column chromatography using 4:1 hexanes:acetone to elute the pure product. The solvent

is removed to afford about 0.8 g (51%) of product. ^{1}H NMR (400 MHz, $CDCl_3$), TLC (1:1 hexanes:EtOAc) R_f=0.8.

Step C

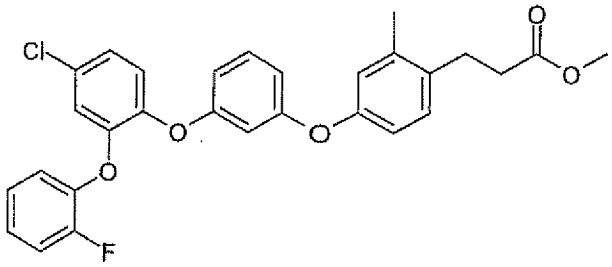
4-Chloro-2-(2-fluoro-phenoxy)-phenol



A solution of 4-chloro-2-(2-fluoro-phenoxy)-benzaldehyde (0.8 g, 3.2 mmol) in chloroform (10 mL) is treated with *m*-CPBA (2.75 g, 16 mmol). The reaction is heated to reflux and stirred for about 2 hr. The reaction is cooled to room temperature and quenched with 10% aqueous $NaHSO_4$. The aqueous is extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate, and the solvent is removed. The crude is diluted in methanol (20 mL) and treated with potassium carbonate (1.32 g, 9.6 mmol). The reaction stirred for 30 minutes at room temperature. The reaction is filtered and the solvent removed. The crude is purified by silica gel column chromatography using 4:1 hexanes:acetone to elute the pure product. The solvent is removed to afford about 0.64 g (84%) of product. ^{1}H NMR (400 MHz, $CDCl_3$). MS (ES-) *m/z* mass calcd for $C_{12}H_8ClFO_2$ 238, found 237 (M -1, 100%).

Step D

3-(4-{3-[4-Chloro-2-(2-fluoro-phenoxy)-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester



A solution of 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (0.66 g, 2 mmol), 4-chloro-2-(2-fluoro-phenoxy)-phenol (0.3 g, 1.3 mmol), copper(I) chloride (0.06 g, 0.6 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (0.06 mL, 0.3

mmol), and cesium carbonate (0.82 g, 2.5 mmol) in NMP (10 mL) is heated to 120°C. The reaction is stirred overnight, and then is cooled to room temperature. The reaction is then quenched with 1N aqueous hydrochloric acid and extracted with ethyl ether. The organic is washed with brine, dried over sodium sulfate, filtered, and the solvent removed. The crude is purified by silica gel column chromatography using 9/1 hexanes/ethyl acetate to elute the pure product. The solvent is removed to afford about 0.072 g (11%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{24}ClFO_5$ 506, found 524 (M + NH4, 100%).

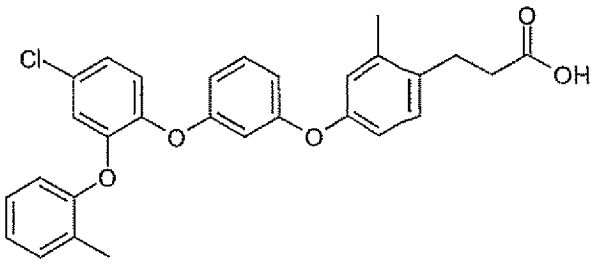
Step E

3-(4-{3-[4-Chloro-2-(2-fluoro-phenoxy)-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid

A solution of 3-(4-{3-[4-chloro-2-(2-fluoro-phenoxy)-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester (72 mg, 0.1 mmol) in MeOH (10 mL) is treated with 5N aqueous sodium hydroxide (0.3 mL). The reaction is heated to reflux and stirred for 2 hr. The reaction is cooled to room temperature and quenched with 1N aqueous HCl to pH=4. The aqueous is extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate and filtered. The solvent is removed to afford about 60 mg (87%) of product. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{28}H_{22}ClFO_5$ 506, found 524 (M + NH4, 100%).

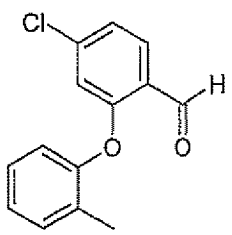
Example 86

3-(4-{3-[4-Chloro-2-(2-o-tolyloxy-phenoxy)-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid



Step A

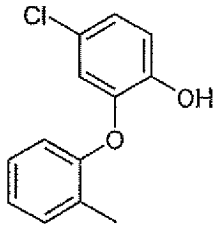
4-Chloro-2-o-tolyloxy-benzaldehyde



The title compound is prepared according to the procedure described in Example 85, Step B by using *o*-cresol. ^{1}H NMR (400 MHz, $CDCl_3$), TLC (1:1 hexanes:EtOAc) R_f=0.8.

Step B

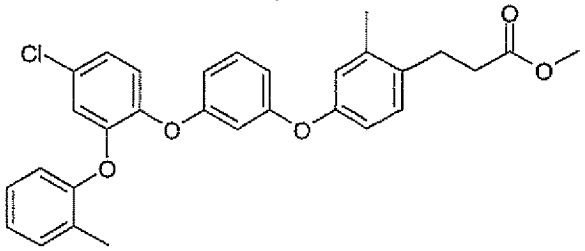
4-Chloro-2-o-tolyloxy-phenol



The title compound is prepared according to the procedure described in Example 85, Step C by using 4-chloro-2-o-tolyloxy-benzaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$). MS (ES-) *m/z* mass calcd for $C_{13}H_{11}ClO_2$ 234, found 233 (M -1, 100%).

Step C

3-{4-[3-(4-Chloro-2-o-tolyloxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester



The title compound is prepared according to the procedure described in Example 85, Step D by using 4-chloro-2-o-tolyloxy-phenol. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{27}ClO_5$ 502, found 520 (M + NH4, 100%).

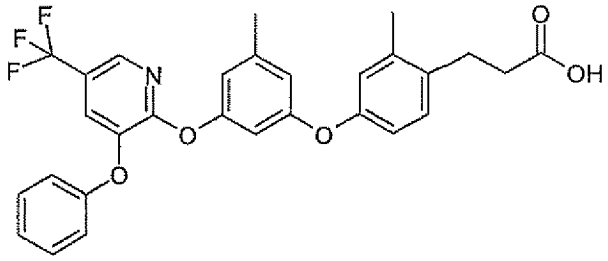
Step E

3-(4-{3-[4-Chloro-2-(2-o-tolyloxy-phenoxy)-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid

The title compound is prepared according to the procedure described in Example 85, Step E by using 3-{4-[3-(4-chloro-2-o-tolyloxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester. ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{25}ClO_5$ 506, found 524 (M + NH4, 100%).

Example 87

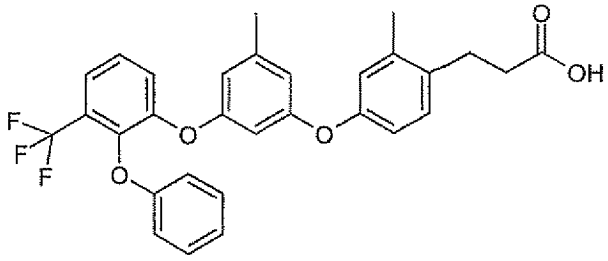
3-{2-Methyl-4-[3-methyl-5-(3-phenoxy-5-trifluoromethyl-pyridin-2-yloxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 85 by using 3-phenoxy-5-trifluoromethyl-pyridin-2-ol and 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford about 32 mg (6%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{24}O_5NF_3$ 523, found 524 (M + 1, 100%).

Example 88

3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-3-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 85 by using 2-phenoxy-3-trifluoromethyl-phenol and 3-[4-(3-bromo-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford about 57 mg (10%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{25}O_5F_3$ 522, found 523 (M + 1, 100%).